Next generation sequencing of pathogens in neonates suspected for sepsis

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Observational pilot study to investigate NGS as a reliable method to identify sepsis in neonates. NGS is proposed as a method to improve clinical identification, diagnosis and stratification of neonatal sepsis and provide basis for a more adequate...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Hepatobiliary neoplasms malignant and unspecified
Study type	Observational non invasive

Summary

ID

NL-OMON48675

Source
ToetsingOnline

Brief title
NGS neonates pilot

Condition

- Hepatobiliary neoplasms malignant and unspecified

Synonym
Infection, Sepsis

Research involving
Human

Sponsors and support

Primary sponsor: Maxima Medisch Centrum
Source(s) of monetary or material Support: investigator initiated;waarbij de hoofdonderzoeker het Vrouwenhof Institute in Germany bereid gevonden heb om in deze

pilotstudie NGS and de analyse op neonatale samples toe te passen zonder extra kosten.

Intervention

Keyword: cfDNA, Neonate, NGS, Sepsis

Outcome measures

Primary outcome

This observational pilot study investigates proof of concept of a well-known technique combined with analysis by bioinformatics, in a new clinical setting.

The primary study parameter is the identification of pathogens with NGS in neonates suspected for sepsis.

Normalized read counts of classified, non-human reads for each plasma sample are calculated, resulting in a quantification of distinct species. To evaluate the significance of read abundances for all species classified, normalized read counts are compared for each species between all septic patients and controls.

To support discrimination by relevance, we will combine abundance and unlikeliness of observed read counts for each species found in a sample.

Species which are significantly represented in a sample with a p value <0.05 compared with controls are considered significant. An individual sepsis indicator quantifier (SIQ) score is calculated as a product of abundance and significance. The SIQ score gives rise to a quantitative and probabilistic assessment of every detected microbe in the respective sample and discriminates signal reads from noise caused by contaminant or commensal species.

Secondary outcome

Not applicable

Study description

Background summary

Neonatal sepsis, a systemic inflammatory response to an infection, is the third leading cause of neonatal mortality and a major public health problem. It is responsible for 13% of all neonatal mortality and 42% of deaths in the first week of life. Recent estimates state a total of 3.0 million cases of neonatal sepsis per year globally with a mortality of 11-19%. The diagnosis of neonatal sepsis is difficult due to several factors: (i) especially in preterm infants, noninfectious conditions that can resemble the symptoms of sepsis are frequent (ii) in contrast to adult sepsis, clear-cut and harmonized sepsis criteria for neonates are lacking or not appropriate (iii) the lack of fast and reliable diagnostic methods, due long turnaround times as well as low sensitivity and specificity from blood culture that represents the current standard of care, and PCR-based assays. However, the fragility of neonatal patients in combination with an immune system utilized with mechanisms aiming for immune tolerance, require immediate actions. Consequently, treatment currently relies on empiric broad-spectrum antibiotic therapy, which is in most cases not adequately matched to the infecting pathogen or precisely timed with respect to the duration of the infection.
This unduly antimicrobial use is itself associated with adverse clinical outcomes due to substantial alterations of the neonatal intestinal flora, increased risks for invasive infections by fungi or drug-resistant bacteria, necrotizing enterocolitis (NEC) and death. New methods and approaches for an early identification of patients suffering from infection together with the identification of the causative microbes are therefore urgently needed to reduce the incidence and mortality of neonatal sepsis.
It is recently shown, that circulating cell-free DNA (cfDNA) from blood plasma of adult septic patients not only is a suitable but a more sensitive and specific analyte to identify pathogens by next-generation sequencing and a bioinformatics workflow coupled with statistic tests to reveal a clinical relevance. NGS-based diagnosis offers many advantages: (i) it is an open platform, providing the opportunity to detect bacterial, fungal and viral pathogens in a single assay, (ii) it is quantitative by counting sequence reads and calculating statistical significances and can therefore potentially discriminate between unspecific colonization/contamination or infection (iii) it provides unbiased and untargeted sequence information on any DNA in patient specimens offering higher sensitivity and specificity.
The aim of this research approach is thus to provide an alternative technology for a timely and untargeted identification of pathogens causing sepsis. Furthermore, a high negative predictive value of the pathogen identification test coupled with fast results on the host*s immune status could lead to reduced antibiotic consumption in this patient collective.
In previous studies, the general applicability and superior reliability of NGS

diagnostics of underlying pathogens from cfDNA over blood culture in adult septic patients could be shown. This promising methodology would be of tremendous value particularly for neonates as being one of the two groups at highest risk at the extremes of age with peak incidence and mortality. Preliminary results to adapt the technology from adult patients cover successful cfDNA isolation and NGS diagnostics from limited plasma volumes to match the considerably smaller blood volumes in neonates. A pilot study with neonates suspected for sepsis is now mandatory to identify pathogens with this technique. Therefore, for example, the algorithms for pathogen identification need to be adapted and trained to detect the differences in bacterial burden and species composition from neonatal plasma samples.

Study objective

Observational pilot study to investigate NGS as a reliable method to identify sepsis in neonates. NGS is proposed as a method to improve clinical identification, diagnosis and stratification of neonatal sepsis and provide basis for a more adequate and targeted therapy for neonates.

Study design

This pilot study is an investigators-initiated study to indicate proof of concept of next generation sequencing of plasma cell-free DNA for the diagnosis of sepsis in neonates. Patients will be enrolled in a monocentre study design at the neonatal department in the Maxima Medical Centre Veldhoven in the Netherlands. Inclusion time will be estimated for 5 months.
NGS is a recently developed technique which will be tested in this pilot study in a new clinical setting. Therefore, 10 patients clinically suspected for sepsis and 10 non-infected patients are enrolled in the study. A blood culture is obtained in infants who are suspected for sepsis and an additional 0.5 ul blood will be obtained for the study. In the non-infected control group in addition to a clinical indication for blood sampling, 0.5 ml blood is obtained.

Study burden and risks

Risks associated with participation are considered negligible and the burden is considered minimal since a research subject is not exposed to an extra puncture besides the clinical indicated puncture to obtain the blood culture. It concerns 0.5 ml extra blood which is nearby 1% of the total blood volume of a neonate born after 26 weeks of gestation with a birth weight of 800 grams. Most infants in the study will be older and have a higher birth weight.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

- Clinical sepsis according to criteria according to Vermont Oxford Neonatal Network:
Apnea, temperature instability, feeding intolerance, worsening respiratory distress or hemodynamic instability.
- Blood culture obtained
- Gestational age above 26 weeks
- Birth weight above 800 gram
For the control group, neonates must be free of infection. Furthermore, a clinical indication for a blood sample must be present. This group will be matched with the cases for AD.

Exclusion criteria

- Gestational age below 26 weeks
- Birth weight below 800 grams
- Antibiotic therapy within 72 hours before blood sampling
- Congenital abnormalities
- Genetic disorders
- Suspected syndromes
- Immunological disorders

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-04-2019
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO Date:	30-10-2018
Application type:	First submission
Review commission:	METC Maxima Medisch Centrum (Veldhoven)
Approved WMO Date:	18-11-2019
Application type:	Amendment

Review commission: METC Maxima Medisch Centrum (Veldhoven)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL66368.015.18
Other	trialregister.nl onder NTR 7400